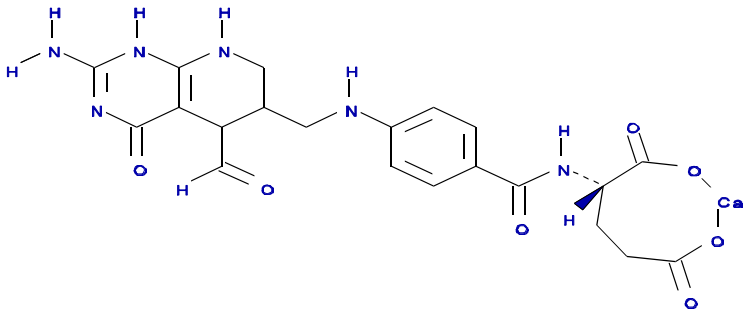
LEUCOVORIN CALCIUM FOR INJECTION

DESCRIPTION

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists.

Also known as folinic acid, Citrovorum factor, or 5-formyl-5,6,7,8 - tetrahydrofolic acid, this compound has the chemical designation of Calcium *N*-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6- pteridinyl)-methyl]amino]benzoyl]-L-Glutamic acid (1:1). Leucovorin calcium has a molecular weight of 511.51 and the following structural formula:



$C_{20}H_{21}CaN_7O_7$

Leucovorin Calcium For Injection is a sterile product indicated for intravenous or intramuscular administration and is supplied in __ mg vials. Each vial contains: [provide information as required in 21 CFR 201.10 and 21 CFR 201.100].

There is 0.004 mEq of calcium per mg of leucovorin.

CLINICAL PHARMACOLOGY

Leucovorin is a mixture of the diasteroisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)-ℓ-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. ℓ-Leucovorin (ℓ-5-formyltetrahydrofolate)

is rapidly metabolized (via 5, 10-methenyltetrahydofolate then 5, 10-methylenetetrahydrofolate) to ℓ,5-methyltetrahydrofolate. ℓ,5-Methyltetrahydrofolate can in turn be metabolized via other pathways back to 5,10 methylenetetrahydrofolate, which is converted to 5-methyltetrahydrofolate by an irreversible, enzyme catalyzed reduction using the cofactors $FADH_2$ and NADPH.

Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Concurrent administration of leucovorin does not appear to alter the plasma pharmacokinetics of 5-fluorouracil. 5-Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication).

Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme.

The pharmacokinetics after intravenous and intramuscular administration of a 25 mg dose of leucovorin were studied in male volunteers. After intravenous administration, serum total reduced folates (as measured by *Lactobacillus casei* assay) reached a mean peak of 1259 ng/mL (range 897 to 1625). The mean time to peak was 10 minutes. This initial rise in total reduced folates was primarily due to the parent compound 5-formyl-THF (measured by *Streptococcus faecalis* assay) which rose to 1206 ng/mL at 10 minutes. A sharp drop in parent compound followed and coincided with the appearance of the active metabolite 5-methyl-THF which became the predominant circulating form of the drug.

The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The area under the concentration versus time curves (AUCs) for ℓ-leucovorin, *d*-leucovorin and 5-methyltetrahydro-folate were 28.4 ± 3.5, 956 ± 97 and 129 ± 12 (mg.min/L ± S.E.). When a higher dose of *d*,ℓ-leucovorin (200 mg/m^2) was used, similar results were obtained. The *d*-isomer persisted in plasma at concentrations greatly exceeding those of the ℓ-isomer.

After intramuscular injection, the mean peak of serum total reduced folates was 436 ng/mL (range 240 to 725) and occurred at 52 minutes. Similar to IV administration, the initial sharp rise was due to the parent compound. The mean peak of 5-formyl-THF was 360 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF increased subsequently over time until at 1.5 hours it represented 50% of the circulating total folates. The mean peak of 5-methyl-THF was 226 ng/mL at 2.8 hours. The terminal half-life of total reduced folates was 6.2 hours. There was no difference of statistical significance between IM and IV administration in the AUC for total reduced folates, 5-formyl-THF, or 5-methyl-THF.

INDICATIONS AND USAGE

Leucovorin calcium rescue is indicated after high dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

Leucovorin calcium is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible.

CONTRAINDICATIONS

Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B_{12}. A hematologic remission may occur while neurologic manifestations continue to progress.

WARNINGS

In the treatment of accidental overdosages of folic acid antagonists, leucovorin should be administered as promptly as possible. As the time interval between antifolate administration (e.g., methotrexate) and leucovorin rescue increases, leucovorin's effectiveness in counteracting toxicity decreases. Do not administer leucovorin intrathecally.

Monitoring the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with

leucovorin.

Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of leucovorin or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously.

Because of the benzyl alcohol contained in certain diluents used for reconstituting Leucovorin Calcium for Injection, when doses greater than 10 mg/m^2 are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP and used immediately (See DOSAGE AND ADMINISTRATION).

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently, the dosage of the 5-fluorouracil must be lower than usually administered. Although the toxicities observed in patients treated with the combination of leucovorin plus 5-fluorouracil are qualitatively similar to those observed in patients treated with 5-fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration in patients treated with the combination.

Therapy with leucovorin and 5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhea must be monitored with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. In a study utilizing higher weekly doses of 5-FU and leucovorin, elderly and/or debilitated patients were found to be at greater risk for severe gastrointestinal toxicity.[1]

PRECAUTIONS

General

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on non-hematologic toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Drug Interactions

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Leucovorin may enhance the toxicity of 5-fluorouracil (see WARNINGS).

Pregnancy: Teratogenic Effects:

"Pregnancy Category C". Adequate animal reproduction studies have not been conducted with leucovorin. It is also not known whether leucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when leucovorin is administered to a nursing mother.

Pediatric Use: See Drug Interactions.

ADVERSE REACTIONS

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following administration of both oral and parenteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin *per se.*

OVERDOSAGE

Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.

DOSAGE AND ADMINISTRATION

Leucovorin Rescue After High-Dose Methotrexate Therapy. The recommendations for leucovorin rescue are based on a methotrexate dose of 12 to 15 grams/m^2 administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information).[2]

Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m^2) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at least once daily. Leucovorin administration, hydration, and urinary alkalinaztion (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). The leucovorin dose should be adjusted or leucovorin rescue extended based on the following guidelines:

GUIDELINES FOR LEUCOVORIN DOSAGE AND ADMINISTRATION
DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY

Clinical Situation	**Laboratory Findings**	**Leucovorin Dosage and Duration**
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).

Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR: a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	150 mg IV q 3 hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe than abnormalities described in the table above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with

methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Impaired Methotrexate Elimination or Inadvertent Overdosage:

Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is a delayed excretion (see WARNINGS). Leucovorin 10 mg/m^2 should be administered IV, IM, or PO every 6 hours until the serum methotrexate level is less than 10^{-8} M. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5 x 10^{-6} M or the 48 hour level is greater than 9 x 10^{-7} M, the dose of leucovorin should be increased to 100 mg/m^2 IV every 3 hours until the methotrexate level is less than 10^{-8}M.

Hydration (3 L/d) and urinary alkalinization with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Megaloblastic Anemia Due to Folic Acid Deficiency:

Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

Preparation:

Each __mg vial of Leucovorin Calcium for Injection when reconstituted with __ mL of sterile diluent yields a leucovorin concentration of __mg per mL. Leucovorin Calcium for Injection contains no preservative. Reconstitute with Bacteriostatic Water for Injection USP, which contains benzyl alcohol, or with Sterile Water for Injection USP. When reconstituted with Bacteriostatic Water for Injection USP, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection USP, it must be used immediately.

Because of the benzyl alcohol contained in Bacteriostatic Water for Injection USP, when doses greater than 10 mg/m^2 are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection USP, and used immediately.

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

-Established name
-Strength and dosage form
-Packaging
-Store at controlled room temperature 15°-30°C(59°-86°F). Protect from light.
-We encourage the inclusion of any applicable NDC numbers and a "CAUTION: Federal law..." statement.

REFERENCES

1. Grem JL, Shoemaker DD, Petrelli NJ, Douglas HO, "Severe and Fatal Toxic Effects Observed in Treatment with High- and Low-Dose Leucovorin Plus 5-Fluorouracil for Colorectal Carcinoma," *Cancer Treat Rep* 1987; 71:1122.

2. Link MP, Goorin AH, Miser AW, *et al*. "The Effect of Adjuvant Chemotherapy on Relapse-Free Survival in Patients with Osteosarcoma of the Extremity." *N Engl J Med* 1986; 314:1600-1606.

Manufactured by:

Revision date.